FORM PTO-1390 (REV 10/94) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO.
0744/077	Unknown 09/341048

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IL98/00012	13 January 1998 (13.01.98)	14 January 1997 (14.01.97)

TITLE OF INVENTION **PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE**

APPLICANT(S) FOR DO/EO/US SAVION, Naphtali; SOLOMON, Arieh

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) (unexecuted).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
    ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    Form PCT/IPEA 408 - PCT Written Opinion
    Form PCT/ISA/220 - PCT Notification of Transmittal of The International Search Report or the Declaration
    Form PCT/ISA/210 - International Search Report
    Form PCT/IPEA/416 - PCT Notification of Transmittal of the International Preliminary Examination Report
    Form PCT/IPEA/409 - PCT International Preliminary Examination Report (w/amended sheets)

Rec'd PCT/PTO 01 JUL 1999

U.S. APPLICATION NO. Unknown 09/341048	INTERNATIONAL APPLICATION NO. PCT/IL98/00012	ATTORNEY'S DOCKET NO. 0744.00077

17. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $930.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $720.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,070.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 98.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 930.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	40 - 20 =	20	X $22.00	$ 440.00	
Independent Claims	2 - 3 =		X $80.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$	
			TOTAL OF ABOVE CALCULATIONS =	$1,500.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
			SUBTOTAL =	$1,500.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
			TOTAL NATIONAL FEE =	$1,500.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28,3.31). **$40.00** per property			+	$	
			TOTAL FEES ENCLOSED =	$1,500.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1,500.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-2185 (0026.023/PCTDO). A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Signature:

SEND ALL CORRESPONDENCE TO.
Customer No.: 002779
BLANK ROME COMISKY & McCAULEY LLP
WIGMAN, COHEN, LEITNER & MYERS IP GROUP
900 - 17th Street, N.W.
Washington, D.C. 20006

Herbert Cohen
NAME

25,109 / July 1, 1999
Registration No. / Date

#3

Small Entity
SMALL BUSINESS CONCERN
Inventor(s): Naphtali Savion and Arieh Solomon

Atty. Docket No.: 0744/077

Serial No. Unknown - U.S. National Phase of PCT/IL98/00012

Filed: July 1, 1999

or

[ ] Filed Herewith

For: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE

SMALL ENTITY FORM - SMALL BUSINESS CONCERN

(VERIFIED STATEMENT/DECLARATION CLAIMING SMALL ENTITY STATUS,
(37 CFR 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am: *(check one)*

[ ] the owner of the small business concern identified below:

[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Ramot University Authority for Applied Research & Industrial Development Ltd.

ADDRESS OF CONCERN P.O. Box 39296, 61392 Tel Aviv, Israel

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled Pharmaceutical Compositions for the Treatment of the Eye by inventor(s) Naphtali Savion and Arieh Solomon described in

(check one)

[ ] the specification filed herewith

[X] U.S. National Phase of PCT/IL98/00012, filed July 1, 1999

[ ] Patent No. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: A separate verified statement is required from each named person, concern or organization having rights to the invention averring to his/her/its status as a small entity. (37 CFR 1.27)

NAME _____

ADDRESS _____

[ ] INDIVIDUAL [X] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee of any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING _____

TITLE OF PERSON OTHER THAN OWNER _____

ADDRESS OF PERSON SIGNING RAANANA RAMAT-GAN

SIGNATURE _____ DATE 11-JUL-99

HANANEL KVATINSKY
Executive Assistant, R & D Division,
Manager, Patent Department

RAMI FINKLER, Ph.D.
President/General Manager

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of	)	
	)	
SAVION et al.	)	
	)	
Serial No. Unknown	)	
National Phase of PCT/IL98/00012	)	
	)	Atty. Dkt. No.: 0744.077
Filed: July 1, 1999	)	HC\pdc
	)	
For: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE	)	

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination and fee calculation, kindly amend the application as follows:

IN THE SPECIFICATION:

Page 1, line 1, insert the following:

--RELATED APPLICATION

This is a U.S. National Phase Application of PCT Application Serial No. PCT/IL98/00012; filed 13 January 1998, which in turn is based on Israeli Application No. 120005, filed 14 January 1997, the priority of which is claimed herein.--.

Page 5, line 22, change "H^3" to --^3H--.

Page 6, delete line 4.

line 5, change "iii" to --ii--, and after "matter" insert --termed *"reconstituted HDL"* and sphinogolipids--.

line 8, change "iv" to ---iii--.

Page 9, line 24, change "the the" to --the--.

Page 12, line 5, change "Lyteer™" to --Lyeteer™--.

line 10, change "Lyteer™" to --Lyeteer™--.

Page 13, line 8, change "and a treated eye" to --and Lyeteers™ treated eye--.

line 9, after "Lipofundin™" insert --treated eye--, and change "close to" to --close to normal--.

line 5, after "phospholipids" insert --

Page 15, line 17, please insert the following --Although certain presently preferred embodiments of the present invention have been specifically described herein, it will be apparaent to those skilled in the art to which the invention pertains that variations and modifications of the various embodiments shown and described herein may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.--.

IN THE CLAIMS:

Please cancel claims 1-71 and replace with the following claims 72-111.:

--~~72~~ 68. A method for the treatment of disorders of the anterior segment of the eye comprising administering to a subject in need of such treatment a composition comprising an agent being high density lipoprotein (HDL).

73. A method according to claim 72, wherein the anterior segment of the eye is the corneal epithelium, stromal conjunctiva, and the glands present in both.

74. A method according to claim 72, wherein the disorders are selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy.

75. A method according to claim 72, wherein the disorders include a decrease in secretion from glands located in the conjunctiva.

76. A method according to claim 75, wherein the disorders are selected from the group consisting of: dry eye and tear film disfunction caused by medication.

77. A method according to claim 72, wherein the disorders are manifested by a slow rate of regeneration of epithelial cells of the anterior segment of the eye.

78. A method according to claim 77, wherein the slow rate of regeneration is caused by old age, or by administration of anti-proliferative substances.

79. A method for the treatment of diseases of the anterior segment of the eye selected from the group consisting of mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; comprising administering to a subject in need of such treatment at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl-ester.

80 . A method according to claim 79, wherein said agent is Lipofundin™

81. A method according to claim 79, wherein said agent is Intralipid™

82. A method according to claim 79, further comprising albumin.

83. A method according to claim 72, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

84. A method according to claim 83, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

85. A method according to claim 83, wherein the sphingolipids are sphingomyelins.

86. A method according to claim 79, wherein the other lipid components of HDL are triglycerides and/or glycerol.

87. A method according to claim 79, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phosopholipids and/or sphinolipids and at least one apolipoprotein.

88. A method according to claim 79, wherein phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

89. A method according to claim 79, wherein the sphingolipids are sphingomyelins.

90. A method according to claim 83, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

91. A method according to claim 86, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

92. A method according to claim 72, further comprising administering a growth factor, an attachment factor or an extracellular matrix component.

93 A method according to claim 79, further comprising administering a growth factor, an attachment factor or an extracellular matrix component..

94. A method according to claim 91, wherein the growth factor is selected from the group consisting of: Keratinocyte Growth Factor (KGF/FGF7); Epidermal Growth Factor (EGF) and other growth factors of the FGF family.

95. A method according to claim 92, wherein the growth factor is selected from the group consisting of Keratinocyte Growth Factor (KGF/FGF7); Epidermal Growth Factor (EGF) and other growth factors of the FGF family.

96. A method according to claim 91, wherein the attachment factor is selected from the group consisting of: laminin and fibronectin.

97. A method according to claim 92, wherein the attachment factor is selected from the group consisting of: laminin and fibronectin.

98. A method according to claim 91, wherein the extracellular matrix components are selected from the group consisting of: collagen and heparan sulfate proteoglycans.

99. A method according to claim 92, wherein the extracellular matrix components are selected from the group consisting of: collagen and heparan sulfate proteoglycans.

100. A method according to claim 72, further comprising an agent capable of providing protection from U.V. radiation.

101. A method according to claim 79, further comprising an agent capable of providing protection from U.V. radiation.

102. A method according to claim 100, wherein the agent capable of providing protection from U.V. radiation is oxybenzone.

103. A method according to claim 101, wherein the agent capable of providing protection from U.V. radiation is oxybenzone.

104. A storage medium for the preservation of isolated cornea comprising at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

ii. a combination of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester.

105. A storage medium according to claim 104, wherein the agent is one or more of the group consisting of:

i. Lipofundin™

ii. Intralipid™

106. A storage medium according to claim 104, further comprising albumin.

107. A storage medium according to claim 104, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

108. A storage medium according to claim 104, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinosital.

109. A storage medium according to claim 104, wherein the sphingolipids are sphingomyelin.

110. A storage medium according to claim 104, wherein the other lipid components of HDL are triglycerides and/or glycerol.

111. A storage medium according to claim 107, wherein the apolipoprotein is selected from the group consisting of Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.--.

REMARKS

Original claims 1-71 in the International case have been cancelled in favor of new claims 72-111.

In the event there are any questions relating to this Amendment or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney.

Please charge any shortage or credit any overpayment of fees to BLANK ROME COMISKY & MCCAULEY LLP, Deposit Account No. 23-2185 (0744.077). In the event that a petition for an extension of time is required to be submitted herewith and in the event that a separate petition does not accompany this report, Applicants hereby petition under 37 C.F.R.

§1.136(a) for an extension of time for as many months as are required to render this submission timely. Any fee due is authorized above.

Respectfully submitted,

BY: ________________________

Herbert Cohen
Registration No,. 25,109

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Date: July 1, 1999

09/341048
80 Rec'd PCT/PTO 01 JUL 1999

PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE

FIELD OF THE INVENTION

The present invention concerns pharmaceutical compositions for the treatment of the eyes and more specifically for the treatment of disorders of the anterior segment of the eye.

BACKGROUND OF THE INVENTION

The protective structures of the anterior surface of the eye include the eyelids, conjunctiva, and the cornea. The posterior surfaces of the lids are covered with a mucous membrane and the palpebral conjunctiva which reflects onto the eye to become the bulbar conjunctiva. The bulbar conjunctival epithelium is continuous with the corneal epithelium which accounts for about 10% of the anterior surface of the eye and is where most of the stationary refraction occurs.

The corneal epithelium is 4-5 cells thick and the superficial cells contain many microvilli. These aid in maintaining the moisture of the epithelial surface by promoting the adhesion of the tear film to the surface. This film lubricates the anterior surface of the eye to decrease the frictional forces arising from the persistent blinking movements of the eyelids, foreign particles on the surface of the eye, and the rotational movements of the eyeball. The tear film also transfers oxygen from ambient air to the cornea.

The anterior surface of the eye is vulnerable to damages inflicted by various causes including mechanical abrasion of the cornea; contact lens wearing; spontaneous peeling of the epithelium; damaged epithelium and stroma following photo-refractive keratectomy; chemical burns; over exposure to ultraviolet light including sunlight; systemic diseases such as Sjogren syndrome, Steven-Johnson syndrome, Cicatricial pemphigoid syndrome; chronic edema of cornea with recurrent erosion of epithelium; impaired tear film formation, and conditions following damage of epithelia due to radial keratotomy.

Aging often causes disorders resulting from slow regeneration of the epithelium. The impaired regeneration and abnormality of the cells causes thinning of the epithelial layer and its impaired adherence to the basal lamina thus decreasing the ability of the cornea to retain the tear film leading to further epithelial damage.

Following injury to the corneal epithelium, nearby cells retract slightly, round up and begin an ameboid migration from the basal layer across the exposed basement membrane to cover the defect with a new monolayer of cells. These cells then take on the characteristics of a new basal layer and undergo mitosis to gradually fill in the defect with the full complement of four to five layers of cells. Present treatment for corneal wounds involves applying eye drops to the surface in order to protect the delicate healing process from erosion due to blinking and the other sources of friction. There are no currently used medicaments that promote the healing process itself. Attempts to administer fibronectin in order to promote healing of persistent defects of the corneal epithelium failed (Fukuda *et al.*, *Am J. Ophthalmol.*, **119**(3):281-287, (1995)).

It would have been highly desirable to provide an ophthalmic composition capable of protecting the corneal epithelium and enhancing its healing and regeneration.

The rate of cell proliferation in many cell types has been correlated with the rate of cholesterol synthesis, and more specifically with the biosynthesis

of various intermediates in the cholesterol biosynthesis pathway and their by-products such as farnesylated proteins and others. Thus, inhibition of an early enzyme in the biosynthesis of cholesterol inhibits cell growth in cultured fibroblasts (McGuire *et al., J. Biol. Chem.*, **268**:22227-22230, (1993)). Factors which cause cholesterol efflux from cells (e.g. high density lipoproteins, HDL) alleviate the negative feedback inhibition of cholesterol synthesis and enhance growth of MDCK cells *in vitro* (Gospodarowicz *et al., J. Cell. Physiol.*, **117**:76-90, (1983)).

The cornea is an avascular organ obtaining nutrition from the vasculature of the limbus by diffusion. At the outer surface of the cornea, the epithelium is essentially isolated from the plasma's large complexes such as HDL which hardly diffuse through the cornea. Thus, HDL which performs the *"reverse cholesterol transport"* from peripheral organs to the liver (Glomset, J.A., *J. Lipid Res.*, **9**:155-167, 1968) is unable to perform this task in the corneal epithelium.

SUMMARY OF THE INVENTION

The present invention is based on the surprising finding that high density lipoprotein (HDL), or a combination of its non-cholesterol lipid constituents (phospholipids, and other lipids such as triglycerides and glycerol), which are capable of forming reconstituted HDL, promotes normal healing and regeneration of damaged eye epithelium.

Both HDL and said lipid constituents were able to initiate the process of healing, to increase its rate, and to promote reversion of the damaged epithelium of the eye to the normal state, i.e. where the damaged area is covered again by layers of epithelial cells.

Thus, the present invention concerns a pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising, as an

active ingredient, at least one agent capable of causing a net efflux of cholesterol from cells, together with an opthalgestically acceptable carrier.

The term *"treatment"* refers to curing of the disorder of the eye, to alleviation of some of the undesired symptomes of various eye disorders, and/or to prevention of various eye disorders before they are manifested.

The term *"anterior segment of the eye"* refers to the corneal and conjunctival epithelium and includes the epithelial cells, as well as the glands present in the epithelium.

The term *"disorders of the anterior segment of the eye"* refers to disorders which cause physical damage to the corneal or conjunctival epithelium, to disorders which decrease the rate of regeneration of cells making up this epithelium, or to disorders causing diminished secretions from glands present in the conjunctival epithelium, or to a combination of some of these disorders.

Typical disorders of the anterior segment of the eye caused by physical or chemical damage are: mechanical abrasion of the cornea, corneal epithelial defects created by wearing contact lenses, corneal epithelial defects created by spontaneous peeling of the epithelium, corneal damage following photo-reactive keratectomy, injuries caused by chemical substances, damage caused by exposure to ultraviolet light, systemic diseases creating damage to the corneal epithelium and conjunctiva, for example, Sjorgren-Syndrome, Steven-Johnson Syndrome, Cicatricial Pemphigoid Syndrome, chronic edema of the cornea with recurrent erosion of epithelium and the like.

Typical disorders of the anterior segment of the eye caused by a decrease in the rate of generation of cells include deterioration of the eye due to old age or an anti-proliferative treatment.

The pharmaceutical composition of the present invention may be administered to persons suffering from disorders which cause damage to the corneal or conjunctival epithelia, or in conjunction with treatments which are known to cause such damage, for example, laser or radial keratectomy or administration of various systemic or topical medications.

The active agents of the invention are those capable of causing a net efflux of cholesterol from cells. Locating candidate agents capable of generating a net cholesterol efflux, may be carried out, for example, by determining the net efflux of labeled cholesterol from cells according to the method described in Naphtali Savion and Shlomo Kotev-Emeth, *Eur. J. Biochem.*, 183:363-370 (1989). Briefly, confluent endothelial or smooth muscle cultures are allowed to incorporate ^{3}H-cholesterol. The candidate to be tested as an effector of cholesterol efflux is then added to the cell culture and the percentage of radioactivity remaining in the cells after 24 hrs. is determined. Candidates which are able to significantly lower the amount of labeled cholesterol in these cells, are those which are capable of serving as active agents in the pharmaceutical compositions of the invention.

Preferably, the present invention concerns a pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising as an active agent at least one compound selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. a composition of matter termed *"reconstituted HDL"* and sphinogolipids comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester; and

iii. at least one HDL Apolipoprotein.

The term *"high density lipoprotein"* refers to lipoproteins which may be isolated from humans or other mammalian sources (e.g. bovine plasma), for example, as specified in Denis Gospodarowicz *"Methods for Preparation of Media, Supplements, and Substrata for Serum-Free Animal Cell Culture"*, pp. 69-86, 1984, Alan R. Liss, Inc., New York, New York or other isolation methods based on the density of the HDL.

The term *"phospholipids"*, refers to phospholipids which naturally occur in HDL such as phosphatidylcholine, phosphatidylserine and phosphatidylinositol. An example of *"sphingolipids"* is sphingomyelin.

The term *"and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester"* refers to glycerides, glycerol and triglycerides. In accordance with the invention glycerides and triglycerides which are not present naturally in HDL, but have an analogous function to glycerides and triglycerides present in HDL may also be used. The composition of matter comprising the non-cholesterol and the non-cholesteryl-ester lipid components of HDL (generally phospholipids, triglycerides and glycerides) is termed *"reconstituted HDL"* (Gillote *et al., J. Biol. Chem.*, 271:23792-23798, 1996). This term refers to a complex comprising phospholipids, triglycerides and glycerides, which differs from natural HDL by the absence of cholesterol, cholesteryl-esters, and apolipoproteins.

Reconstituted HDL particles are prepared by the chelate dispersion/Bio-Bead removal technique (Sparks *et al., J. Biol. Chem.* **267**:25830-25838, 1992). Typically, compounds which are used in intravenous nutrition as a source of essential fatty acids, are suitable for serving as the lipid components of HDL. Example being Intralipid™, (Pharmacia AB, Sweden), Lipofundin™ (Braun Melsungen AG, Germany) and others.

The term *"HDL apolipoproteins"* refers typically to apolipoprotein A-I, A-IV and E-apolipo-proteins or a combination thereof, either isolated from a human or mammalian source (Savion and Gamliel, *Arteriosclerosis*, **8**:178-186, 1988). Apolipoprotein-E is purified according to Wernette-Hammond *et al., J. Biol. Chem.*, **264**:9094-9101, 1989. The HDL apolipoproteins may also be prepared by various genetic engineering methods described in Breslow, *et al., Proc. Natl. Acad. Sci.*, **79**:6861-6865, 1982. For example: Human Apolipoprotein A-I gene can be prepared according to the method of Karathanasis *et al., Proc. Natl. Acad. Sci.*, **80**:6147-6151, 1983; Human Apolipoprotein A-IV gene according to Elshourbagy, *et al., J. Biol. Chem.*, **262**:7973-7981, 1987; and Human Apolipoprotein E gene according to Das, *et al., J. Biol. Chem.*, **260**: 6240-6247, 1985; Paik, *et al., Proc. Natl. Acad. Sci.*, **82**:3445-3449, 1985.

The composition of the present invention may further comprise albumin.

Albumin is the most abundant plasma protein and serves as the plasma carrier of free fatty acids. Each albumin molecule has 27 binding sites for fatty acids. Albumin may thus serve as a scavenger for toxic free fatty acids released by damaged anterior chamber tissue included in reconstituted HDL.

The pharmaceutical compositions of the invention may further comprise other ingredients having ophthalgesic affects, especially those which are known to facilitate healing and regeneration of cornea and conjunctiva such as growth factors, for example, keratinocyte growth factor (KGF/FGF7), or

epidermal growth factor (EGF) and other growth factors of the EGF family known in the art; various attachment factors such as laminin or fibronectin, and extracellular matrix components such as collagen, heparan sulfate proteoglycans and others.

The pharmaceutical compositions of the invention may also include agents capable of providing ultraviolet light protection, such as oxybenzone 3%, and other such preparations known in the art.

The pharmaceutical compositions of the invention should be administered in the form of eye drops or eye salves together with opthalgestically acceptable carriers. The composition may be in the form of an emulsion, micelles liposomes, etc. The concentration of the active ingredients in the composition should be in the range of 0.1-20%, preferably 0.2-10%, most preferably 0.2-2%.

Some disorders of the eye that are to be treated by the pharmaceutical compositions of the invention include diminished liquid clearance from the eye causing water retention which eventually leads to the rupture of the eye membranes. In such cases, it is preferable that the compositions of the invention be presented in a hyperosmotic formulation which can serve to draw excess liquid from the eye. Such hyperosmotic formulation may be formed, for example, by the addition of NaCl to the composition.

By another aspect, the invention comprises a method for the treatment of disorders of the anterior segment of the eye comprising administering to a subject in need of such treatment at least one agent capable of causing a net efflux of cholesterol from cells.

By another aspect, the invention comprises use of at least one agent capable of causing a net efflux of cholesterol from cells for the preparation of a medicament for the treatment of disorders of the anterior segment of the eye.

By yet another aspect, the present invention concerns a storage preparation for storing and maintaining isolated corneas, for example, in an eye

bank. In order to maintain the viability of epithelial cells as well as the exposed endothelium of the eye, it is preferable to add to the storage medium an effective amount of at least one agent capable of causing a net efflux of cholesterol from cells, as explained above.

The invention now will be illustrated with reference to some non-limiting drawings and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows fluorescein staining of untreated damaged eye cornea 5 days after surgery (x 16);

Fig. 2 shows fluorescein staining of untreated damaged eye cornea 12 days after surgery (x 16);

Fig. 3A shows the histological appearance of normal cornea;

Fig. 3B shows the histological appearance of untreated damaged eye cornea 12 days after surgery;

Fig. 4 shows fluorescein staining of damaged eye cornea following Intralipid™ treatment;

Fig. 5 shows the histological appearance of damaged eye cornea following Lyteers™ treatment;

Fig. 6 shows fluorescein staining of damaged eye cornea after 3 days of treatment with HDL;

Fig. 7 shows fluorescein staining of damaged eye cornea at the end of treatment with HDL;

Fig. 8 shows the histological appearance of damaged eye cornea after HDL treatment;

Fig. 9 shows the histological appearance of damaged eye cornea following 7 days of treatment with Lipofundin™; and

Fig. 10 shows the histological appearance of damaged eye cornea following 7 days of treatment with Lyeteers™.

DETAILED DESCRIPTION OF THE INVENTION

I. Experimental Procedures

A. Animal model of corneal epithelium and conjunctival epithelium damage

A rabbit model for keratoconjunctivitis (Gilbard *et al., J. Inv. Ophthal. Vis. Sci.*, **2**:225-228 (1987)) was used with slight modification. Surgery performed on anesthetized rabbits using a surgical microscope (Inami, Japan) involved excision of the plical fold over the eye, occlusion of the lacrimal duct, and peeling of the palpebral and bulbar conjunctiva. This surgery was done on one eye of 20 rabbits of average age 3 months of both sexes. Surgery and all subsequent treatments were done in accordance with ARVO rules for animal care in research. Tear film osmolarity is elevated by postoperative day 1. Corneal epithelial glycogen levels decline progressively, and conjunctival goblet cell density decreases. These pathologies lead to corneal epithelium damage covering the entire corneal surface by the fifth postoperative day, and it was at this time that treatment of the eyes commenced.

B. HDL preparation

HDL was prepared from human plasma by differential ultracentrifugation flotation (*Havel et al.*, "Distribution and chemical composition of ultracentrifugally lipoproteins in human serum", *J. Clin. Invest.*, **34**:1345-53. (1995)).

C. Evaluation of Rabbit Cornea

Lesions in fluorescein stained corneas were clinically evaluated by biomicroscopy using a slit lamp (Haag Streit, Switzerland) with cobalt filter illumination. Photography of the fluorescein staining was taken with a slit lamp mounted camera (Topcon, Japan). At the end of each experiment, the rabbits were

sacrificed and the cornea were excised, fixed in paraformaldehyde and examined for epithelial lesions.

D. Histological examination

At the end of the treatment, the rabbits were sacrificed by a lethal dose of intravenously injected pentobarbitone. The eyes were enuclated and the corneas fixed in 4% paraformaldehyde. Corneas were embedded in paraffin blocks, sectioned, and with hematoxylin-eosine for light microscope examination.

II. Treatment of corneal epithelium damage caused by conjunctival epithelium damage

Example 1

Rabbits with cornea damage induced as above were treated as follows: Five rabbits were treated with commercially available artificial tears (Lyteers™), five rabbits were treated with HDL (1mg protein/ml) in phosphate buffered saline, five rabbits were treated with a commercially available lipid mixture (10% Intralipid™: 10% soybean oil, 1.2% egg phospholipids, 2.2% glycerol), and two rabbits were left untreated. Treatment consisted of applying two drops to the eye 3 times a day for seven consecutive days. The eyes were evaluated clinically during the experiment and pictures were taken every other day of the fluorescein stained corneas.

Fluorescein staining of damaged eyes 5 and 12 days following surgery is shown in Figs. 1 and 2, respectively. As can be seen, the surface of the untreated eye became progressively more scratched and opaque with time leading eventually to blurred vision.

Histological staining of damaged eye is shown in Fig. 3B and is compared to histological staining of normal eye 3A. As can be seen, in the damaged eye there has been complete erosion of the exposed epithelium due to

persisant rubbing of the epithelium by the lids as well as severe keratitis and vascularization of the cornea.

Animal eyes that were treated with Intralipid™ show complete reversal to normal morphological structure as indicated by fluorescein staining (Fig. 4). However, animal eyes treated with Lyeteers™, (Fig. 5) (commercially available artifical tears composed mainly of water and a viscous substance) did not return to normal. In contrast to normal eyes, the damaged area did not become covered again with normal layers of cuboidal epithelial cells and a single top layer of wing cells, but was covered instead by only a single layer of wing cells. These results indicate that artificial tears such as Lyeteers™ cannot promote regeneration of normal eye epithelium.

In contrast to this, animal eyes treated with HDL showed essentially a complete return to normal morphological structure as indicated by fluorescein staining taken on the third day (Fig. 6) and at the end of treatment (Fig. 7) as well as by histological staining (Fig. 8). Histological staining shows essentially a complete return to normal of the eye epithelium characterized by formation of several layers of cuboidal cells and a single top layer of wing cells.

These results clearly indicate that both HDL and Intralipid™ are able to promote healing and regeneration of damaged eye epithelium and return to normal epithelium.

Example 2

Three rabbits underwent central corneal peeling of the epithelium in both eyes. The area of peeling, 8 mm in diameter, was first demarcated with trephine, and the epithelium excised with a scalpel. The right eye of each rabbit was treated with two drops of Lipofundin™ 10% three times a day, while the left eye was treated with the same dose of Lyeteers™. The cornea were stained with fluorescein and photographed immediately after epithelium removal and on the third and fifth day afterwards. On the seventh day, the rabbits were sacrificed by a lethal dose of pental and the corneas were excised, fixed and stained for light microscopy. The denuded area in the fluorescein and fixed corneas was determined, and the extent of remaining damage calculated as the remaining denuded area divided by the initial denuded area. The results appear in Table 1 below which gives the fraction of initial damage remaining 0, 3, 5, and 7 days after peeling the epithelium. The results show that the rate of healing was faster in the Lipofundin™ treated eyes. Figs. 9 and10 show the epithelium of a Lipofundin™ treated eye and Lyeteers™ treated eye, respectively, after 7 days of treatment. Whereas the Lipofundin™ appears close to normal, in the Lyeteers™ treated eye the epithelium still appears thin, immature, and containing only flat and wing cells which have migrated to the denuded area.

Table 1

	Treatment	
Time (Days)	Lipofundin™	Lyeteers™
0	1.00	1.00
3	.304	.378
5	.036	.107
7	0	0

CLAIMS:

1. A pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising an ophthalgestically acceptable carrier and as an active ingredient an agent being high density lipoprotein (HDL).

2. A pharmaceutical composition according to Claim 1, wherein the anterior segment of the eye is the corneal epithelium, stromal conjunctiva, and the glands present in both.

3. A pharmaceutical composition according to Claim 1, wherein the disorders are selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy.

4. A pharmaceutical composition according to Claim 1, wherein the disorders include a decrease in secretion from glands located in the conjunctiva.

5. A pharmaceutical composition according to Claim 4, wherein the disorders are selected from the group consisting of: dry eye and tear film disfunction caused by medication.

6. A pharmaceutical composition according to Claim 1, wherein the disorders are manifested by a slow rate of regeneration of epithelial cells of the anterior segment of the eye.

7. A pharmaceutical composition according to Claim 6, wherein the slow rate of regeneration is caused by old age, or by administration of anti-proliferative substances.

8. A pharmaceutical composition for the treatment of diseases of the anterior segment of the eye selected from the group consisting of mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; recurrent erosion of epithelium; comprising an ophthalgestically acceptable carriers and as an active ingredient at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl-ester.

9. A pharmaceutical composition according to Claim 8, wherein said agent is Lipofundin™

10. A pharmaceutical composition according to Claim 8, wherein said agent is Intralipid™

11. A pharmaceutical composition according to Claim 1 or 8, further comprising albumin.

12. A pharmaceutical composition according to Claim 1 or 8, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

13. A pharmaceutical composition according to Claim 8 or 12, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

14. A pharmaceutical composition according to Claim 8 or 12, wherein the sphingolipids are sphingomyelins.

15. A pharmaceutical composition according to Claim 8, wherein the other lipid components of HDL are triglycerides and/or glycerol.

16. A pharmaceutical composition according to Claim 12, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

17. A pharmaceutical composition according to Claims 1 to 8, further comprising a growth factor, an attachment factor or an extracellular matrix component.

18. A pharmaceutical composition according to Claim 17, wherein the growth factor is selected from the group consisting of: Keratinocyte Growth Factor (KGF/FGF7), Epidermal Growth Factor (EGF) and other growth factors of the FGF family.

19. A pharmaceutical composition according to Claim 17, wherein the attachment factor is selected from the group consisting of: laminin and fibronectin.

20. A pharmaceutical composition according to Claim 17, wherein the extracellular matrix components are selected from the group consisting of: collagen and heparan sulfate proteoglycans.

21. A pharmaceutical composition according to Claims 1 to 8, further comprising an agent capable of providing protection from U.V. radiation.

22. A pharmaceutical composition according to Claim 21, wherein the agent capable of providing protection from U.V. radiation is oxybenzone.

23. A method for the treatment of disorders of the anterior segment of the eye comprising administering to a subject in need of such treatment a composition comprising an agent being high density lipoprotein (HDL).

24. A method according to Claim 23, wherein the anterior segment of the eye is the corneal epithelium, stromal conjunctiva, and the glands present in both.

25. A method according to Claim 23, wherein the disorders are selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial

defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy.

26. A method according to Claim 23, wherein the disorders include a decrease in secretion from glands located in the conjunctiva.

27. A method according to Claim 26, wherein the disorders are selected from the group consisting of: dry eye and tear film disfunction caused by medication.

28. A method according to Claim 23, wherein the disorders are manifested by a slow rate of regeneration of epithelial cells of the anterior segment of the eye.

29. A method according to Claim 28, wherein the slow rate of regeneration is caused by old age, or by administration of anti-proliferative substances.

30. A method for the treatment of diseases of the anterior segment of the eye selected from the group consisting of mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; recurrent erosion of epithelium comprising administering to a subject in need of such treatment at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl-ester.

31. A method according to Claim 30, wherein said agent is Lipofundin™

32. A method according to Claim 30, wherein said agent is Intralipid™

33. A method according to Claim 23 or 30, further comprising albumin.

34. A method according to Claim 23 or 30, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

35. A method according to Claim 30 or 34, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

36. A method according to Claim 30 or 34, wherein the sphingolipids are sphingomyelins.

37. A method according to Claim 30, wherein the other lipid components of HDL are triglycerides and/or glycerol.

38. A method according to Claim 34, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

39. A method according to Claims 23 to 30, further comprising administering a growth factor, an attachment factor or an extracellular matrix component.

40. A method according to Claim 39, wherein the growth factor is selected from the group consisting of: Keratinocyte Growth Factor (KGF/FGF7), Epidermal Growth Factor (EGF) and other growth factors of the FGF family.

41. A method according to Claim 39, wherein the attachment factor is selected from the group consisting of: laminin and fibronectin.

42. A method according to Claim 39, wherein the extracellular matrix components are selected from the group consisting of: collagen and heparan sulfate proteoglycans.

43. A method according to Claims 23 to 30, further comprising an agent capable of providing protection from U.V. radiation.

44. A method according to Claim 43, wherein the agent capable of providing protection from U.V. radiation is oxybenzone.

45. Use of high density lipoprotein (HDL) for the preparation of a medicament for the treatment of disorders of the anterior segment of the eye.

46. Use according to Claim 45, wherein the anterior segment of the eye is the corneal epithelium, stromal conjunctiva, and the glands present in both.

47. Use according to Claim 45, wherein the disorders are selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy.

48. Use according to Claim 45, wherein the disorders include a decrease in secretion from glands located in the conjunctiva.

49. Use according to Claim 48, wherein the disorders are selected from the group consisting of: dry eye and tear film disfunction caused by medication.

50. Use according to Claim 45, wherein the disorders are manifested by a slow rate of regeneration of epithelial cells of the anterior segment of the eye.

51. Use according to Claim 50, wherein the slow rate of regeneration is caused by old age, or by administration of anti-proliferative substances.

52. Use of at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl-ester;

for the preparation of a medicament for treatment of disorders of the anterior segment of the eye selected from the group consisting of mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; with recurrent erosion of epithelium.

53. Use according to Claim 52, wherein said agent is Lipofundin™

54. Use according to Claim 52, wherein said agent is Intralipid™

55. Use according to Claim 45 or 52, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

56. Use according to Claim 52 or 55, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

57. Use according to Claim 52 or 55, wherein the sphingolipids are sphingomyelins.

58. Use according to Claim 52, wherein the other lipid components of HDL are triglycerides and/or glycerol.

59. Use according to Claim 55, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

60. A storage medium for the preservation of isolated cornea comprising at least one agent selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids; and

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester.

61. A storage medium according to Claim 60, wherein the agent is one or more of the group consisting of:

i. Lipofundin™

ii. Intralipid™

62. A storage medium according to Claims 60 and 61, further comprising albumin.

63. A storage medium according to Claim 60, wherein the HDL is human HDL, bovine HDL, or reconstituted HDL comprising of phospholipids and/or sphinolipids and at least one apolipoprotein.

64. A storage medium according to Claim 60 or 63, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinosital.

65. A storage medium according to Claim 60 or 63, wherein the sphingolipids are sphingomyelin.

66. A storage medium according to Claim 60, wherein the other lipid components of HDL are triglycerides and/or glycerol.

67. A storage medium according to Claim 63, wherein the apolipoprotein is selected from the group consisting of Apolipoprotein A-I and Apolipoprotein A-IV or a combination of both apolipoproteins.

FIG. 1

FIG. 2

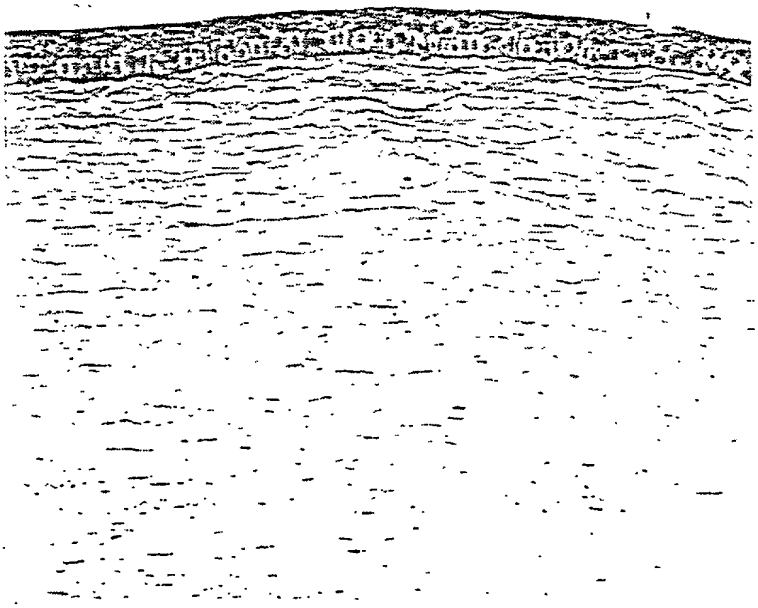

FIG.3A

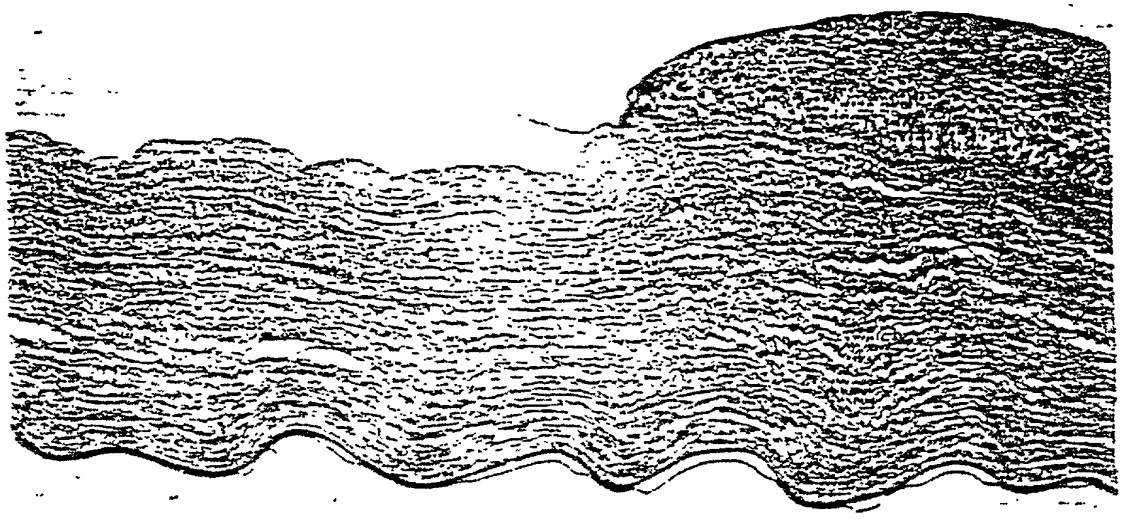

FIG. 3B

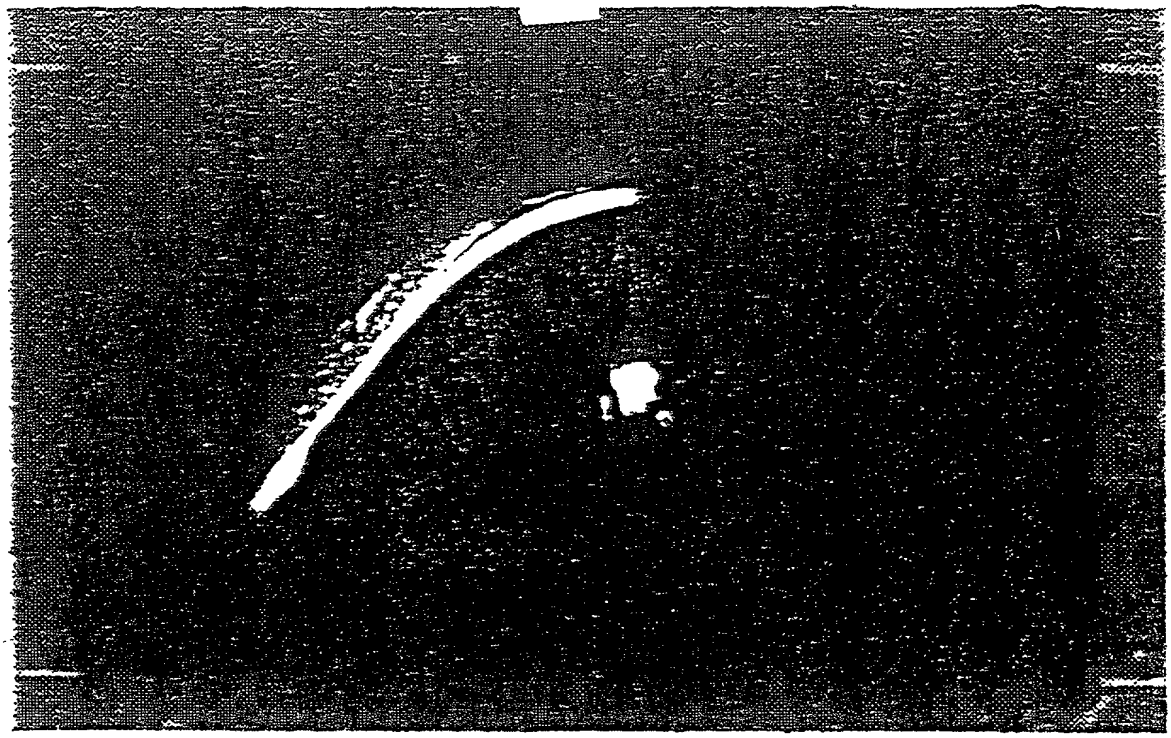

FIG. 4

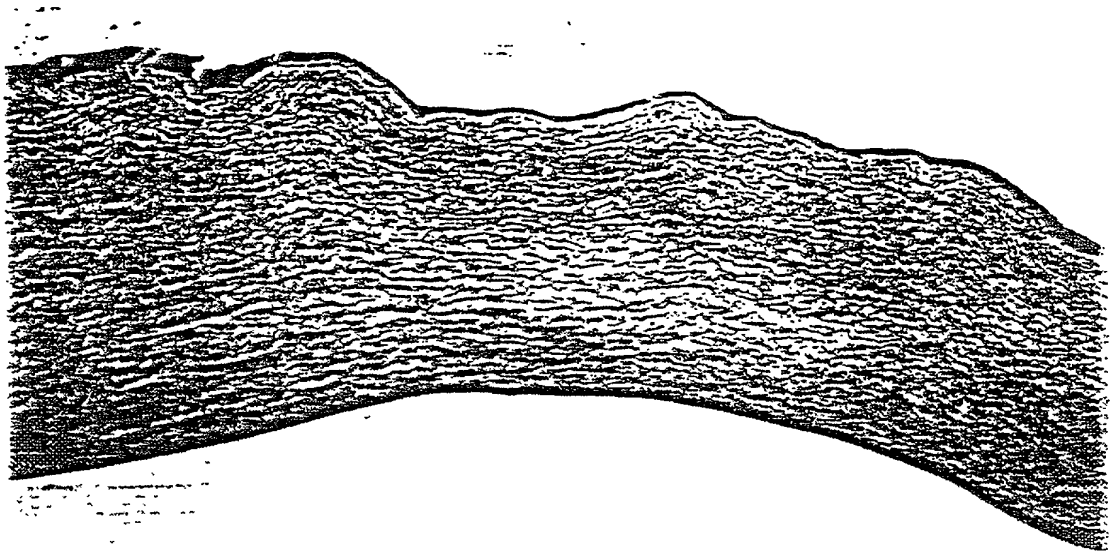

FIG. 5

FIG. 6

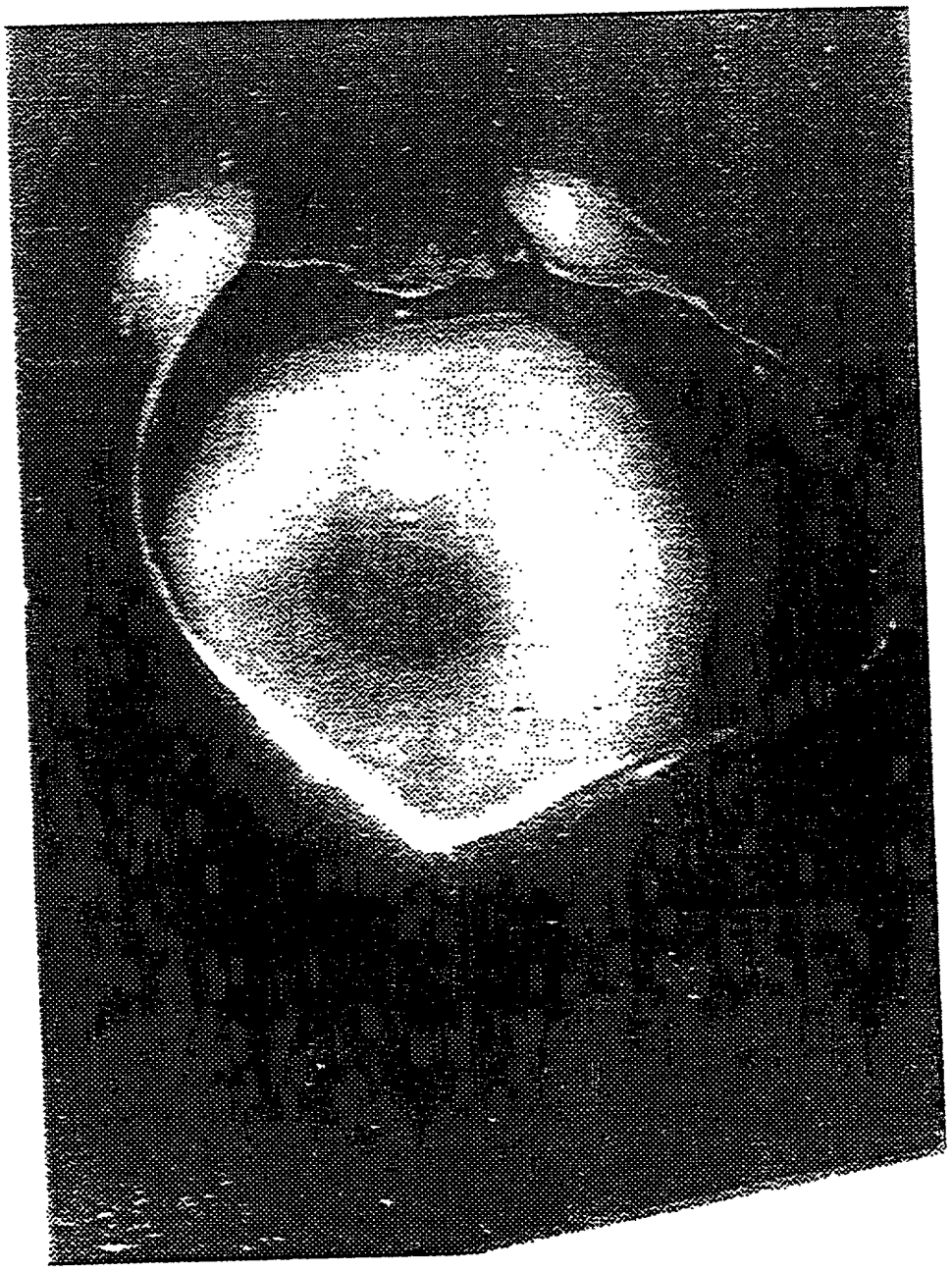

FIG. 7

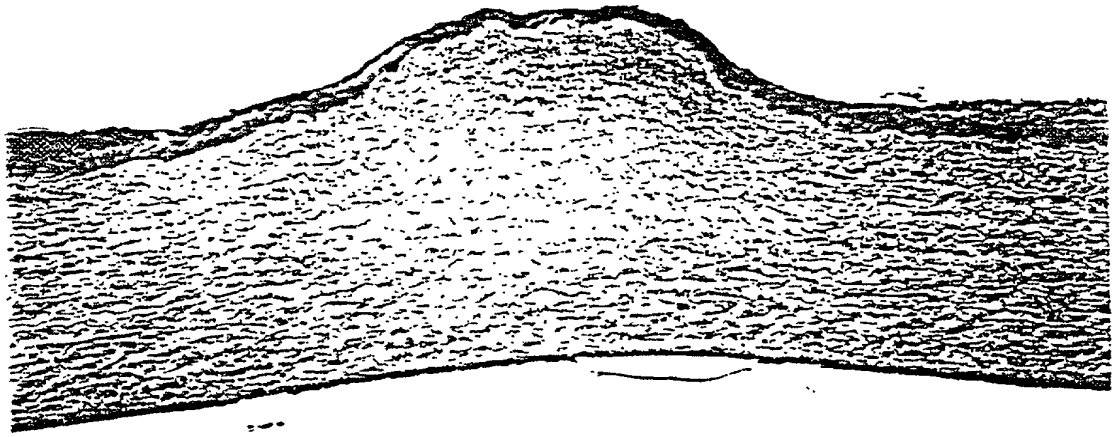

FIG. 8

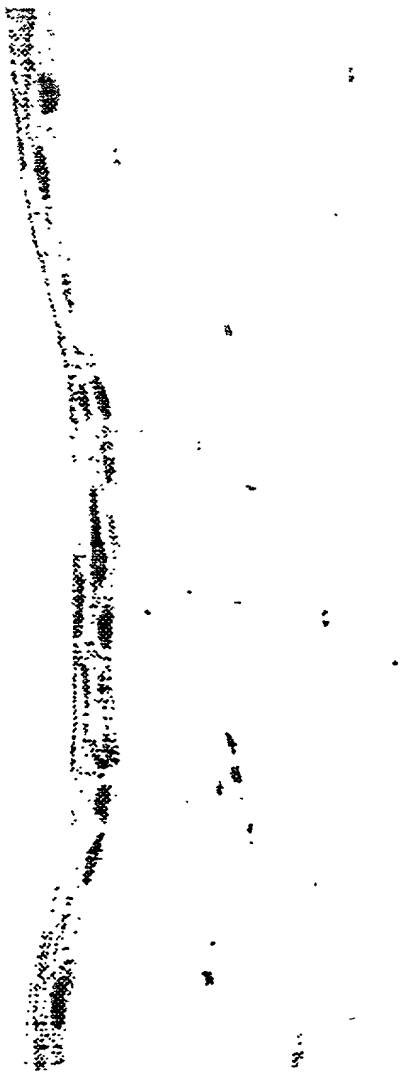

FIG. 9

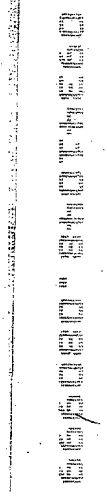

FIG. 10

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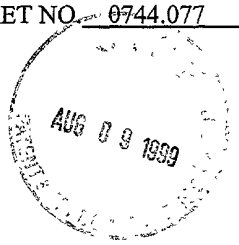

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE

the specification of which is attached hereto unless the following box is checked:

[ ] was filed on July 1, 1999 as United States Application Number or PCT International Application Number _____ and was amended on _____(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NUMBER	COUNTRY	(DAY/MONTH/YEAR FILED)	PRIORITY NOT CLAIMED
120005	ISRAEL	14 JANUARY 1997	☐
			☐

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Declaration For Patent Application (Continued) Atty. Dkt. No. 0744.077

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NUMBER	FILING DATE	STATUS -- PATENTED, PENDING, ABANDONED
PCT/IL98/00012	13 January 1998	Pending

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: Herbert Cohen, Reg. No. 25,109; Victor M. Wigman, Reg. No. 25,201; George C. Myers, Jr., 27,040; Saul Leitner, Reg. No. 22,283; Donald R. Greene, Reg. No. 22,470; Michael C. Greenbaum, Reg. No. 28,419; Michael D. White, Reg. No. 32,795; Paul J. Riley, Reg. No. 38,596; Karl O. Neidert, Reg. No. 39,313; and Jonathan M. Cohen, Reg. No. P-40,562.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature:	Date:
Residence:	Citizenship:
Post Office Address:	

Full name of fourth joint inventor (given name, family name):	
Inventor's signature:	Date:
Residence:	Citizenship:
Post Office Address:	